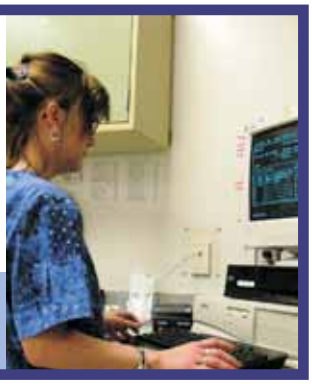
REX

Laboratory Bulletin

February 2004

UPDATES AND INFORMATION FROM REX PATHOLOGY LABORATORY

Issue Number 88



Intraductal Carcinoma of Breast: Pathologic Challenges and the New Van Nuys Prognostic Index

Intraductal carcinoma of the breast refers to an *in situ* carcinoma of the mammary duct system, often referred to as duct(al) carcinoma *in situ* (DCIS). DCIS is not a single disease. The biologic behavior and management vary considerably depending on the histologic appearance of the lesion, size/extent of the disease process, and the completeness of surgical excision. Depending on the combination of these factors present in a given case, treatment options can range from excisional biopsy to mastectomy (with or without radiation therapy). Prior to widespread adoption of screening mammography, most cases of DCIS were detected clinically (mass or nipple discharge), possessed an unfavorable histology, and often had extended for a considerable distance within the mammary duct system at the time of presentation. Such cases often required mastectomy or whole breast irradiation to assure local control. Mammography has resulted in the identification of more cases of low grade DCIS of small size, which are more suitable candidates for breast conserving surgery or localized radiotherapy. This variability challenges all physicians (radiologists, surgeons, pathologists, medical oncologists, and radiation oncologists) participating in the care of patients with DCIS. The University of Southern California/Van Nuys Prognostic Index (VNPI) has been proposed as a classification system, which can provide a means of standardizing therapy in DCIS patients. [1] Others have pointed out that the USC/VN approach to DCIS patients differs from that in many other medical centers and that the index may not be generally applicable. [2,3] The Rex Pathology Dept. has been providing a VNPI score on breast biopsies with DCIS for several years to assist in the management of these patients.The original VNPI evaluated 3 parameters: histopathologic classification, tumor size, and margin width. Recently patient age was added to the VNPI.[1] All four parameters are given equal weight and are assigned between 1 – 3 points to provide a score ranging from 4 – 12 (Table 1).

Table 1 - Revised Van Nuys Prognostic Index [1]

Score Score	Pathologic Classification	Tumor Size (mm)	Margin Width(mm)	Age (year)
1	Non-high grade without necrosis	<15	10	>61
2	Non-high grade with necrosis	16 - 40	1 - 9	40 - 60
3	High grade	>41	<1	<39

Based on the total score, further management of the patient is based on the guidelines present in Table 2.

Table 2 – Treatment Guidelines Based on VNPI [1]

VNPI Score	Suggested Treatment
4 - 6	Excision alone
7 - 9	Excision plus radiation therapy
10 - 12	Mastectomy

Sounds pretty simple, right?

Pathology Challenge #1 - Find the lesion

While DCIS may present as a palpable mass, it is more often discovered as a mammographic abnormality or incidental finding. The gross appearance of the biopsy is frequently not helpful. Punctate foci of creamy white semi-solid material may be observed in high grade DCIS with necrosis (resulting in adoption of the term "comedo" carcinoma for such lesions). Most cases of DCIS produce no visual or palpable clues – the tissue looks grossly normal – to both the surgeon and the pathologist. For needle or mammatome biopsies, the entire specimen is submitted for microscopic examination and multiple levels are reviewed. For small (e.g. 3–5 cm.) biopsies – the entire specimen is submitted. For larger biopsies, the pathologist

(continued on page 2)

Rex Pathology Associates, P.A.

Stephen V. Chiavetta, MD (919) 784-3060
Timothy R. Carter, MD (919) 784-3058
John D. Benson, MD (919) 784-3059
John P. Sorge, MD (919) 784-3062
Keith V. Nance, MD (919) 784-3286
Vincent C. Smith, MD (919) 784-3056
Rhonda Humphrey, Practice Manager (919) 784-3063

REX LABORATORY SERVICES
Healthcare for life. Your life.

generally selects areas for microscopic examination. In biopsies prompted by a mammographic abnormality, it is important to try to correlate the gross appearance of the biopsy with the mammographic findings. At times we get a biopsy with the history of only "abnormal mammogram". The thoughtful surgeon will alert the pathologist with the specifics of the abnormality (e.g. microcalcifications vs. density).The biopsy specimen radiograph should be submitted to the pathology laboratory along with the tissue. The Rex Radiology Dept. highlights the abnormalities for us on such radiographs. Again, for small biopsies, the entire specimen will be submitted for microscopic examination. This is not practical for larger biopsies (> 6-7 cm) performed for **diagnosis** of an abnormal mammogram. (We sometimes see biopsies in the range of 10–12 x 6-8 cm from patients with abnormal mammograms.)For a large specimen with microcalcifications, a repeat specimen radiograph after the specimen has been sliced in 3–4 mm. thick sections, permits careful localization of all mammographically suspicious microcalcifications to assure these areas will be examined microscopically. For large specimens with a suspicious mammographic density, the gross evaluation by the pathologist, aided by the mammographic findings, are critical in trying to identify the mammographic lesion. Most breast biopsies (80-90%), whether prompted by clinical or mammographic findings, are benign. Microcalcifications are commonly found in cysts, sclerosing adenosis, ancient fibroadenomas, as well as otherwise unremarkable breast lobules or stroma. Mammographic densities/clinically firm masses may be the result of cysts, fibroadenomas, radial scars, or the contrast between mammary adipose tissue and fibroglandular tissue. The **primary concern** of the pathologist initially is to find the abnormality (if any exists in the biopsy). The smaller the biopsy, the easier it is to find (cf. diagnose) the abnormality. For large biopsies, if a malignancy (e.g. DCIS) is identified in tissue that appeared grossly normal, remaining tissue can be submitted for microscopic examination to determine the extent of the disease.

Pathology Challenge #2 – Classify the disease

In most instances, the pathologic diagnosis of DCIS is relatively straightforward, particularly for high-grade ("comedo") lesions (Fig. 1). While DCIS may have a variety of architectural patterns (e.g. solid, papillary, cribriform) – it is the nuclear features which determine the grade. High grade DCIS has large nuclei with a vesicular chromatin pattern and prominent nucleoli. Low grade DCIS has smaller nuclei with condensed chromatin and small/absent nucleoli. The VNPI stratifies low grade DCIS into two categories: low grade with necrosis (Fig. 2) and low grade without necrosis (Fig. 3).

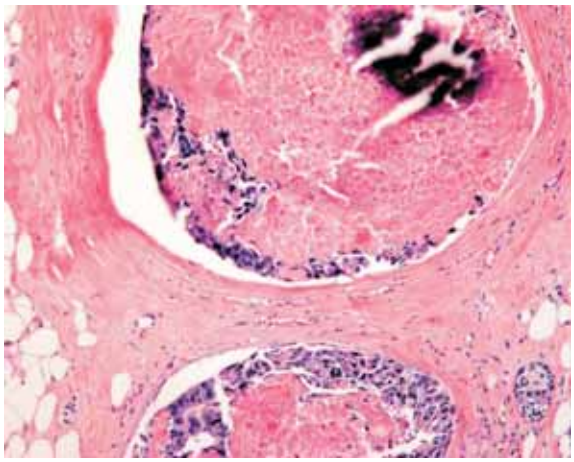


Figure 1: High grade ("comedo") DCIS - note large microcalcification (VNPI score of 3)

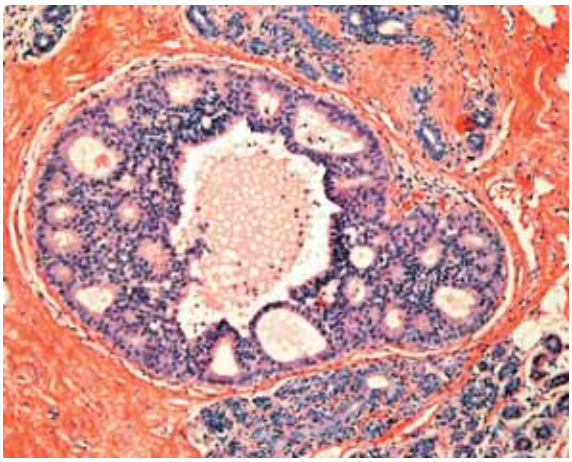


Figure 2: Low grade DCIS with necrosis (VNPI score of 2)

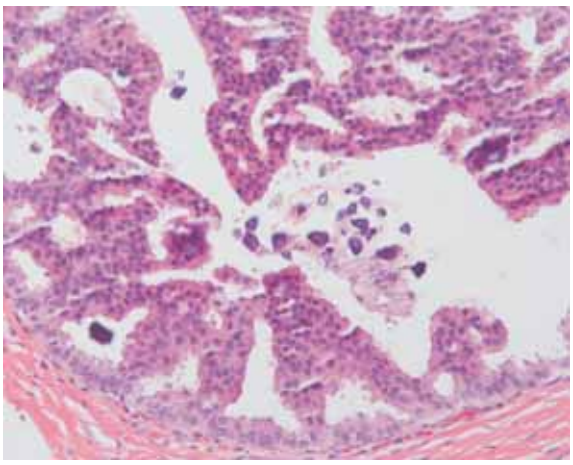


Figure 3: Low grade DCIS w/o necrosis – note microcalcifications (VNPI score of 1)

(continued on page 3)

The distinction between low grade DCIS and atypical duct hyperplasia (ADH) can be difficult at times, particularly on small biopsies. ADH is currently regarded as a lesion, which predicts an increased generalized risk of subsequent breast cancer (in either breast) in the patient, while low grade DCIS is regarded as a true precursor to cancer in the immediate locale of its occurrence. While sharing histologic similarities to low grade DCIS, ADH usually occupies an area less than 3 mm and is confined to a single lobular unit. [5] Nevertheless occasional cases can produce divergent interpretations, even among "expert" breast pathologists. [6] For this reason, the finding of "ADH" on a needle/mammatome biopsy will frequently result in the recommendation for an excisional biopsy to exclude the possibility of low grade DCIS.

Pathology Challenge #3 – Determine tumor size

This parameter of the VNPI is the most difficult to determine.[1] As noted earlier, DCIS is often imperceptible to visual inspection or palpation. DCIS is a 3-dimensional disease, but microscopic slides present a 2-dimensional plane of the lesion. In cases where only 1-2 foci of DCIS are observed, 2 dimensions can be measured on the glass slide(s). For cases where the DCIS is present on multiple slides, size determination is more problematic. For small biopsies, an attempt can be made to estimate the size of the lesion based on the prevalence of DCIS in the sections and the size of the biopsy. For large biopsies, this is not practical for most pathology departments (see discussion above). *The USC/VN group submits the entire specimen completely as sequential sections with detailed mammographic mapping.This labor-intensive practice has not been widely adopted and represents an important difference to bear in mind if one is contemplating use of the VNPI.* At times, radiographic calcifications may provide a more objective estimate of the lesion size, although correlation with the histologic findings is needed.

Pathology Challenge #4 – Margins (a no-win situation)

After finding the lesion, classifying it, and measuring it – the pathologist is asked to determine whether the margins of excision are involved or "free". Margins can be assessed in 2 ways – by perpendicular (radial) sections or tangential sections. There are limitations to each method. Perpendicular margins allow one to measure the distance between the tumor and the margin (*a requirement of the VNPI*), but they permit evaluation of only a fraction of the true margin. As a result, perpendicular margins are vulnerable to a "false negative" margin assessment (figs.4-5).

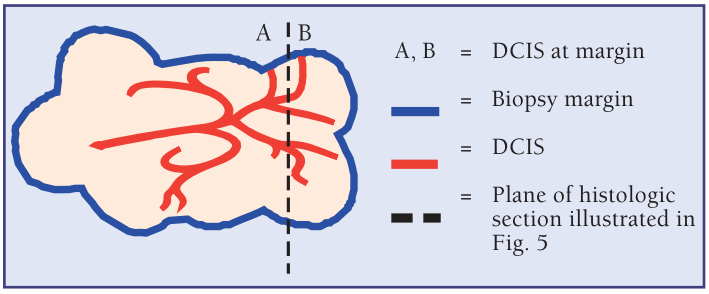


Figure 4: Perpendicular margin section

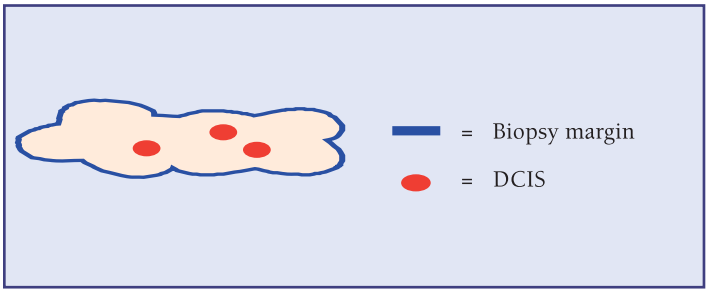


Figure 5: Microscopic Appearance of Perpendicular Margin Section(False Negative Margin Assessment)

Tangential margins permit evaluation of a much greater area of the margin surface. * (see colored box on next page) However, because the tissue block is usually at least 3 mm. thick – and must be "faced" by a microtome to achieve a cutting surface suitable for mounting a tissue section on a slide – a "false positive" margin may result (figs. 6-7).

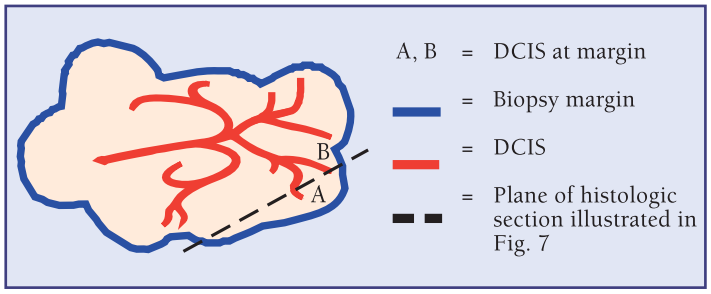


Figure 6: Tangential margin section

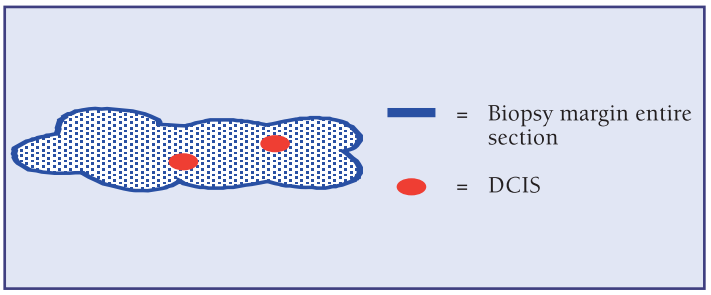


Figure 7: Microscopic Appearance of Perpendicular Margin Section(False Positive Margin Assessment)

(continued on page 4)

Both approaches to margin assessment have their supporters and detractors ("less filling" vs. "tastes great"). The perpendicular margin approach is particularly well suited for recognizable masses (e.g. invasive carcinoma) and has been the standard surgical pathology approach to margin assessment for decades. As noted above, it is the approach used in the VNPI. Tangential margins are useful for diseases, which are difficult to visualize and possess an uneven, or "geographic" margin (e.g. use of Moh's technique for basal cell carcinoma of the skin). As with many things in medicine, an increase in sensitivity leads to a loss of specificity and *vice versa*. The author uses both types of assessment. For diagnostic biopsies – I rely on perpendicular margins. For "re-excisions" or lumpectomies, I use both types depending on the disease type, the size of the specimen, and the urgency with which an answer is needed. (It takes me longer to "gross in" a specimen with tangential margins. If a surgeon requests immediate feedback on gross margin assessment, I will "ink" the external margins and section the specimen – using perpendicular sections for microscopic evaluation.)

* Consider a standard histologic section to be 3x2 in diameter with a thickness of 5 microns (0.0005 cm). If one of the 3 cm. edges is a margin (perpendicular margin), the surface area of the margin assessed by that microscopic section would be 3 cm x 0.0005 cm = 0.0015 cm^2. If that 3x2 section was a tangential margin, the surface area of the margin assessed would be 3 cm x 2 cm = 6 cm^2. A "lumpectomy" evaluated by 6 perpendicular margins would evaluate 6 x 0.0015 cm^2 = 0.0009 cm^2, while a lumpectomy evaluated by 6 tangential margins would evaluate 6x 6 cm^2 = 36 cm^2 (a 40,000-fold difference).[4]

Conclusions

Despite the problems discussed in this article, I believe pathologists, here and elsewhere, provide valuable information to assist in the clinical management of DCIS patients. I also believe that it is helpful for clinicians to be aware of the challenges DCIS imposes upon pathologists trying to characterize the disease into categories such as the VNPI. The VNPI provides a useful classification scheme to assist in patient management, but care must be taken in extrapolating the experience of one (albeit well respected) multidisciplinary group to our medical community. Effective immediately, the Rex pathologists will update the VNPI on DCIS cases to include age – as well as the other parameters discussed above. *Caveat medicus.*

John D. Benson, MD

The author is indebted to the Rex Breast Center radiology staff for accommodating (often untimely) requests for "repeat specimen radiographs", to Dr. John Sorge for providing the photographic images, and to Mitzi Sherwood (IT Graphics) for superb assistance with the illustrations.

References

1. *Silverstein MJ. An argument against the routine use of radiotherapy for ductal carcinoma in situ. Oncology 17: 1511-1532, 2003.*
2. *Wickerham DL. The Silverstein article reviewed. Oncology 17:1539-42, 2003.*
3. *Prosnitz LR, Marks LB. The Silverstein article reviewed. Oncology 17:1544-1546, 2003.*
4. *Carter D. Evaluation of margins and processing of specimens (lecture notes) Diagnosis and Management of Breast Pathology: A Multimodal Approach (Am. Soc. Clin. Pathol.) December 5-7, 2002.*
5. *Page DL, Jensen RA, Simpson JF. Premalignant and malignant disease of the breast: the roles of the pathologist. Mod Pathol 11:120-8, 1998.*
6. *Rosai J. Borderline epithelial lesions of the breast. Am J Surg Pathol 15:209-21, 1991.*

Updates and Information from Rex Outreach Services

What the well dressed blood collection tubes are wearing this spring...

For the convenience of our Outreach clients, Rex Outreach Laboratory requisitions come with "peel and stick" labels to facilitate labeling of specimen tubes. When applying a specimen label to the tube, please align the label along the long axis of the tube as shown in the picture. (Please do not apply the label in a spiral fashion or like a belt around the center of the tube.) This will facilitate processing of the specimen and result in faster availability of results.

Rex Healthcare Laboratory (919) 784-3040. Telephone extensions are: Pathologists' Direct Line (3063), Sharon Logue (Lab Director 2400), Robin Ivosic (Outreach and Microbiology Lab Manager 3053), Elaine Patterson (Core Lab Manager 3054), Jackie Okoth (Core Lab PM Manager 4248), Diane Young (Anatomic Pathology Manager 3888), Nga Moore (Customer Service Manager 3396), Diane Stephenson (Blood Bank Manager 4767), Justin Hodges (Blood Plan Manager 4750).
Client Response Center (919) 784-6000 (phone), (919) 784-6299 (fax)